



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D.C. 20460

EPA-SAB-EC-90-003

OFFICE OF  
THE ADMINISTRATOR

November 28, 1989

Mr. William Reilly  
Administrator  
US Environmental Protection Agency  
Washington, D.C. 20460

Dear Mr. Reilly:

In 1988 the Agency asked the Science Advisory Board to review two documents: "A Cancer Risk-specific Dose Estimate for 2,3,7,8-TCDD" and "Estimating Exposure to 2,3,7,8-TCDD". In response, the SAB Executive Committee (EC) appointed a "Dioxin" Panel, co-chaired by Dr. Bernard Goldstein of the Robert Wood Johnson Medical School and Dr. Nancy Kim of the New York State Department of Health. The Panel conducted a public meeting in November, 1988 to review the documents. On October 24, 1989, Dr. Kim presented the attached report to the EC, which was approved by the EC.

The EC believes that the "Dioxin" Panel has done an outstanding job of reviewing two very fine Agency documents. Both the Panel and the Agency are to be congratulated on their efforts, neither of which was easy, given the lack of scientific consensus and the heightened public concern surrounding the topic.

It should be noted that the "Dioxin" Panel was not asked, nor did it choose, to address directly or in detail the adequacy of the Agency's 1985 cancer risk assessment for 2,3,7,8-TCDD. However, in the course of the current review, the Panel generally agreed with the EPA Working Group's criticism of the linear multi-stage model as applied to the specific case of 2,3,7,8-TCDD in 1985.

This criticism reflects, in part, the existence of a series of important and innovative mechanistically oriented studies which have provided new insight into the toxicological effects of 2,3,7,8-TCDD and related compounds. The EC joins the Panel in encouraging the Agency to support research which will incorporate this new information into risk assessment approaches currently under development, where appropriate.

The EC concludes that the existing, LMS-based risk assessment for 2,3,7,8-TCDD lacks a firm scientific foundation. However, until the new approaches are fully developed and peer-reviewed, estimates based on other models are equally questionable. Unfortunately, the direction and extent of any change from the LMS-based risk estimate that might result from the application of more appropriate models cannot be determined at this time.

The Panel was favorably impressed by the exposure document. They found that indirect routes of exposure, via food chain contamination, result in higher exposures to the general population than do direct environmental exposures. This exposure model-based conclusion has important implications and should be tested by comparing predictions with environmental measurements.

The SAB appreciates the opportunity of addressing these important, but difficult, questions. We look forward to the Agency's formal response to this review.

Sincerely,

*Raymond C. Loehr*  
Raymond C. Loehr, Ph.D.  
Chair, Executive Committee  
Science Advisory Board



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

November 28, 1989

OFFICE OF  
THE ADMINISTRATOR

Dr. Raymond C. Loehr  
Chairman  
Executive Committee  
Science Advisory Board (A-101F)  
U.S. Environmental Protection Agency  
401 M Street, S.W.  
Washington, D.C. 20460

Subject: Science Advisory Board's Dioxin Panel review of documents from the Office of Research and Development relating to the risk and exposure assessment of 2,3,7,8-TCDD.

Dear Dr. Loehr,

The Ad Hoc Panel on Dioxin of the Science Advisory Board's Executive Committee met in Washington, DC on November 29-30, 1989 to review two draft documents on 2,3,7,8-TCDD: "A Cancer Risk-Specific Dose Estimate for 2,3,7,8-TCDD" (including appendices) and "Estimating Exposure to 2,3,7,8-TCDD".

The Panel concluded that both documents were carefully constructed, well written, and represented a significant effort on the part of EPA to document and explain how the hazard and exposure scientific data have been analyzed. The Panel in particular commends the EPA Dioxin Working Group for having alertly initiated an analysis of the extent to which new scientific information concerning 2,3,7,8-TCDD can be factored into risk assessment.

The Panel's review focused on the scientific validity of the statements and judgments in the documents as they were written. The Panel has not reviewed the process by which EPA arrived at the judgments expressed in these documents; nor has it concerned itself with the degree of unanimity of the EPA Working Group. A specific written charge from EPA or the EPA Science Advisory Board was received by the Panel.

The Panel has taken into account the oral comments made to the public during the course of the committee meeting. It has

also listened to a review prepared by EPA staff of the written comments received by EPA concerning its document. Subsequent to the November 29-30, 1988 meeting, copies of written public submissions were received from EPA and reviewed individually by Panel members.

Understanding the biological effects of the dioxins presents one of the most intriguing challenges in modern biology. Research in this area has been particularly exciting for the insights it has given into exposure assessment, including the role of bioavailability, and for its potential for linking receptor interactions with modern toxicology, including the mechanism of carcinogenesis. While there was extensive discussion of these active research areas, the Panel did not lose sight of the fact that it had a relatively prosaic task: the provision of advice concerning the scientific adequacy of documents.

#### Cancer Risk Document

The document "A Cancer Risk Specific Estimate for 2,3,7,8-TCDD" contains the background and rationale for the EPA Working Group's new risk specific dose for 2,3,7,8-TCDD. In order to help focus its review, the Panel chose to summarize the Cancer Risk document as containing five key points. These points, and the Panel's response, are as follows:

1. The Panel generally agrees with the EPA Working Group's criticism of the Linearized Multistage Model. While there are promising alternative models which may be expected to more accurately reflect the biological basis of 2,3,7,8-TCDD carcinogenesis, such newer models need to be further developed and validated.
2. The Panel agrees that since the determination by EPA of a risk specific dose of 0.006 pg/kg/day in 1985, no new information has appeared to permit reevaluation of the risk specific dose through the use of the standard Linearized Multistage Model approach (i.e. there are neither new long term animal studies nor epidemiologic studies which appropriately could be used to recalculate the risk specific dose using the previous model).
3. The Panel fully agrees that a series of important and exciting mechanistically oriented studies have provided much new insight into the toxicological effects of 2,3,7,8-TCDD and related compounds, and that such information is likely to be of major significance to regulatory decisions concerning 2,3,7,8-TCDD. There has been a parallel increase in the understanding of cancer biology. The Panel commends EPA for reviewing

this information in relation to calculating the risk specific dose for 2,3,7,8-TCDD carcinogenesis.

4. The Panel does not agree with the EPA Working Group's contention that the new scientific information concerning 2,3,7,8-TCDD mandates a change in the 1985 risk specific dose of 0.006 pg/kg/day. The panel did not evaluate the validity of the 1985 risk specific dose.
5. As there is no reason to necessarily believe that a new mechanism model would lead to a relaxation of the risk specific dose for 2,3,7,8-TCDD-induced cancer, in the absence of a validated model suitable to recalculate a risk specific dose, the Panel does not concur with the EPA Working Group's "science policy" decision to change the risk specific dose. Further, the Panel agrees with the EPA document that there is no specific scientific pathway that would allow determination of the extent to which such a change might occur. The Panel therefore finds no scientific basis at this time for the proposed change in risk specific dose for the causation of cancer by 2,3,7,8-TCDD.

The Panel thus concluded that at the present time the important new scientific evidence about 2,3,7,8-TCDD does not compel a change in the current assessment of the carcinogenic risk of 2,3,7,8-TCDD to humans. EPA may for policy reasons set a different risk specific dose number for the cancer risk of 2,3,7,8-TCDD, but the Panel finds no scientific basis for such a change at this time. The Panel does not exclude the possibility that the actual risks of dioxin-induced cancer for humans may be less than or greater than those currently estimated by the Agency using a linear extrapolation approach.

EPA is strongly urged to build upon their excellent review of the new scientific data relevant to 2,3,7,8-TCDD carcinogenesis by moving rapidly to develop and validate a new risk model capable of more accurately estimating the risk of human cancer caused by the dioxins and related compounds. Other recommendations by the Panel, including a need for further focus on reproductive effects and for enhanced use of exposure data in epidemiologic studies, are detailed in the Panel report which is attached.

The Panel also urges EPA to remain abreast of advances in our knowledge of 2,3,7,8-TCDD, particularly at the mechanistic level, and to continue oversight of relevant epidemiological findings as these become available in the peer-reviewed literature.

## Exposure Document

The Panel found that the exposure document, "Estimating Exposure to 2,3,7,8-TCDD" was an improvement over the 1984 assessment because it includes new data, expands consideration of pathways, and addresses additional phenomena. For the most part, it is a credible document and is one of the better documents of this type. The most important implication of the current exposure document is that for the general population indirect routes of exposure-- that is dietary inputs--predominate. Therefore, site-specific assessments should focus on indirect routes of exposure and research efforts should be directed toward confirming predictions with environmental measurements.

The exposure document's Executive Summary is excellent. Several points from that Executive Summary should be emphasized and reiterated throughout the report. For example, when assessing actual sites, whatever monitoring data are available should be used and are preferable to the estimation methods in the document. The Panel emphatically agrees with this statement. The Panel also recommends that the document point out that the best method of measuring human intake is to monitor people and that biological monitoring should be used when possible. These data will establish general exposure and identify subsets of the population (i.e., fish eaters, small children, people with pica) who may have elevated exposures above background levels.

The Panel has a number of significant criticisms of the Exposure document. These include the need to distinguish between excellent versus poor experimental data; the need for careful interpretation of soil-to-plant ratio data in considering uptake of 2,3,7,8-TCDD by plants; the need to more thoroughly describe the magnitude of exposure due to ingestion of food from grazing animals; and a concern that the two incinerator cases in the scenarios are not representative of the average case. Among the recommendations by the Panel, in addition to a greater focus on indirect routes of exposure, are that where possible EPA should validate its models with environmental monitoring; that there should be a consideration of individual activities which might lead to particularly high exposure; that more emphasis is needed on the recommendation to rely more on field sampling data and less on dispersion modeling results; that the commendable account of uncertainty analysis be made even more quantitative; and that, in agreement with EPA, the development of a physiologically based pharmacokinetic model for 2,3,7,8-TCDD is a high priority despite some limitations in the models proposed in the exposure document.

In summary, the Panel strongly encourages the Agency to follow up on this excellent start. There is much new data pertinent to understanding and quantifying the risk due to the presence of 2,3,7,8-TCDD in the environment. Developing and

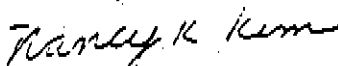
validating new models for human exposure and for cancer and non-cancer risk endpoints can and should be accomplished in the relatively near future by pursuing an active research program in this area.

We appreciate the opportunity to conduct this particular scientific review.

Sincerely,



Bernard D. Goldstein  
Chairman  
Ad Hoc Dioxin Panel



Nancy Kim  
Co Chair  
Ad Hoc Dioxin Panel



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D.C. 20460

FEB 12 1990

THE ADMINISTRATOR

Raymond C. Loehr, Ph.D.  
Chair, Executive Committee  
Science Advisory Board  
U.S. Environmental Protection Agency  
Washington, D.C. 20460

Dear Ray:

Thank you for your November 28, 1989, letter which forwarded the Science Advisory Board (SAB) Dioxin Panel's review of two documents from the Office of Research and Development (ORD) relating to risk and exposure assessment of 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD). The Agency appreciates the work of both the Dioxin Panel and the Executive Committee in carrying out their respective reviews and providing their insightful comments.

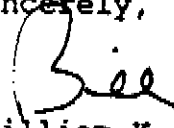
I was very pleased to see the extent to which the SAB reviewers agreed with the EPA working group on many of the difficult issues presented by the 2,3,7,8-TCDD data base. The discussion by the SAB of the science supporting the Risk Specific Dose (RSD) for 2,3,7,8-TCDD was especially helpful. The combined views of the EPA working group and the SAB reviewers have clearly defined for the agency the areas of scientific consensus and the areas where such a consensus has not yet been achieved.

The comments of the Panel on the document entitled, "A Cancer Risk Specific Estimate for 2,3,7,8-TCDD," have been forwarded to the authors of that document. In addition, discussions have already begun within the Agency's Risk Assessment Council both to address work necessary to develop alternative approaches to modeling potential cancer risk associated with 2,3,7,8-TCDD exposure, as suggested by the Panel, and to consider the Panel's comments on the science policy approach to selecting a risk-specific dose for 2,3,7,8-TCDD presented in the Agency's draft document.

The comments of the Panel on the document entitled, "Estimating Exposure to 2,3,7,8-TCDD," have been forwarded to the Office of Health and Environmental Assessment in ORD for consideration during revision of that document. The complementary nature and important substance of these comments will encourage Agency staff to make significant improvements in this already well-received document.

I will provide a more detailed response on the Agency's disposition of your comments in the next few months as the Risk Assessment Council and ORD bring their deliberations on these documents to a close. Thank you again for your efforts in reviewing these two documents.

Sincerely,

  
William K. Reilly



**EPA**

**U.S. Environmental  
Protection Agency**

**Washington, DC  
EPA-SAB-EC-90-003**

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**Report of the ad hoc Dioxin Panel  
of the Science Advisory Board**

**Review of Draft Documents: "A Cancer  
Risk-Specific Dose Estimate for 2,3,7,8  
TCDD" and "Estimating Exposure to  
2,3,7,8 TCDD"**

U.S. EPA  
Science Advisory Board  
Ad Hoc Dioxin Panel

REVIEW OF DRAFT DOCUMENTS

"A CANCER RISK-SPECIFIC DOSE ESTIMATE FOR

2,3,7,8-TCDD

AND

"ESTIMATING EXPOSURE TO 2,3,7,8-TCDD"

## Table of Contents

1.0	Executive Summary	3
2.0	Introduction	3
3.0	Comments on EPA's Draft Document "A Cancer Risk-Specific Dose Estimate for 2,3,7,8-TCDD"	3
3.1	General Comments	4
3.1.1	The Adequacy of the Linearized Multistage Model	5
3.1.2	The Availability of New Information For Use in the LMS Model	5
3.1.3	Mechanistically Oriented Research	5
3.1.4	Relaxation of the Risk Specific Dose for TCDD Carcinogenesis	6
3.1.5	Change of the Risk Specific Dose for TCDD Carcinogenesis	6
3.2	Comments on Specific Issues	6
3.2.1	Mechanisms	8
3.2.2	Research Needs	8
3.2.3	Development and Selection of a Model	10
3.2.4	Toxicology of Related Compounds	10
3.2.5	Epidemiology	11
3.2.6	Pharmacokinetics	11
3.2.7	Reproduction and Immuno-Toxicity	11
4.0	Comments on EPA's Draft Document "Estimating Exposure to 2,3,7,8-TCDD"	12
4.1	Overall Comments on EPA's Draft Exposure Document	12
4.2	Comments on Specific Issues	13
4.2.1	Use of the Best Data	13
4.2.2	Pathways of Exposure	14
4.2.3	Indirect Exposure	14
4.2.4	Scenarios	16
4.2.5	Exposure and Epidemiology	16
4.2.6	Estimating Exposure in the Absence of Empirical Data	17
4.2.7	Rely More on Field Sampling Data and Less on Dispersion Modeling Results	18
4.2.8	Verifiable Exposure Estimates	18
4.2.9	Incorporation of the Most Reliable Exposure Assessment Information	18
4.2.10	Rigorous Characterization of Uncertainty	18
4.2.11	Pharmacokinetics	19

## 1.0 Executive Summary

(same as enclosed cover letter)

## 2.0 Introduction

On November 29-30, 1988 an Ad Hoc Panel of scientists was convened by the EPA Science Advisory Board to review the June, 1988 external review drafts of a series of EPA documents concerning 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD): "A Cancer Risk-Specific Dose Estimate for 2,3,7,8-TCDD" (including Appendices) prepared by an interoffice EPA Workgroup chaired by Dr Peter Preuss of the Office of Research and Development; and "Estimating Exposure to 2,3,7,8-TCDD" prepared by the Exposure Assessment Group under the direction of Dr. Michael Callahan.

The Panel, chaired by Dr. Bernard Goldstein, functioned in part as two separate subpanels, one of which focused on the cancer risk document and the other, chaired by Dr. Nancy Kim, on the exposure document. During part of the time the subpanels met separately. At other times a plenary session was held at which each subpanel had the opportunity to offer comments on both of the documents. However, responsibility for the written critique of the two documents was independently assigned to each of the subpanels.

The Panel's review focused on the scientific validity of the statements and judgments within the documents. To a lesser extent, the Panel also reviewed the appendices as free standing scientific documents. The review of these appendices took into account EPA statements that the appendices served as background documents and did not necessarily represent the EPA Working Group's collective judgment as to the science.

Understanding the biological effects of the dioxins presents one of the most intriguing challenges in modern biology. Research in this area has been particularly exciting for the insights it has given into exposure assessment, including the role of bioavailability, and in its potential for linking receptor interactions with modern toxicology, including the mechanism of carcinogenesis. The Panel strongly commends EPA for initiating a review of this information and for considering the implications of this new data to issues central to the regulation of TCDD. We recommend that EPA's evaluation of the risks of dioxin be an ongoing process as new data on hazard and exposure are published.

## 3.0 Comments on EPA's Draft Document "A Cancer Risk-Specific Dose Estimate for 2,3,7,8-TCDD"

The Subpanel reviewing the cancer risk document consisted of

Dr. Linda Birnbaum; Dr. Marilyn Fingerhut; Dr. Thomas Gasiewicz; Dr. David Gaylor; Dr. Bernard Goldstein, chair; Dr. David Hoel; Dr. Daniel Krewski; Dr. Ellen Silbergeld and Dr. Thomas Starr. Dr. Michael Gallo served as a scientific advisor to the subpanel and contributed written comments. Extensive written comments were also received from Dr. Dennis Paustenbach, a member of the Exposure Subpanel, who could not attend the Panel meeting.

### 3.1 General Comments

In order to help focus its review, the Committee chose to summarize the key points made by EPA in the Cancer Risk document into five statements as follows:

- a) Although the EPA Working Group believes that in many ways the Linearized Multistage Model (LMS) is not a satisfactory approach, present information does not permit choice of an alternative model.
- b) Since the determination by EPA in 1985 of a risk specific dose (RSD) for TCDD of 0.006 pg/kg/day, the EPA Working Group believes that no new information has appeared to permit reevaluation of the RSD using the LMS model (i.e. there are no new long term animal studies which appropriately could be used to recalculate the RSD, and the epidemiological findings are not currently adequate for performance of a risk assessment).
- c) A series of important and exciting mechanistically oriented studies have provided much new insight into the toxicological effects of 2,3,7,8-TCDD and related compounds which are highly relevant to regulatory decisions concerning these compounds. There has been a parallel increase in the understanding of cancer biology relevant to TCDD carcinogenesis.
- d) This new information concerning the mechanism of action of 2,3,7,8-TCDD leads the EPA Working Group to believe that the 1985 RSD of 0.006 pg/kg/day is too stringent.
- e) As there is not a mechanism model suitable to recalculate a specific RSD, the EPA Working Group has made a "science policy" decision to relax the RSD, and have chosen a result using an order of magnitude number reflecting the extent of uncertainty. The EPA Working Group's document makes it clear that there is no specific scientific pathway that will allow determination of the extent to which such a change should occur.

The Panel in general agrees with the first three points above, although differing to some extent in detail and in emphasis. As described in more detail below, the Panel agrees that there are many problems inherent in using the LMS model for TCDD, agrees that there is no currently available alternate validated model, agrees that there are no new studies which could be used to recalculate the risk specific dose with the LMS model, and agrees that there is exciting new data about the mechanism of action of TCDD that points toward the development of a new model suitable for estimating the risk specific dose for TCDD carcinogenesis. However, the Panel does not agree that this new information necessarily leads to a belief that the 1985 RsD of 0.006 pg/kg/day is too stringent. This is the crucial point of disagreement with the EPA Working Group. As the Panel does not concur with the assumption that a new mechanism model of TCDD carcinogenesis would necessarily result in a relaxation of the risk specific dose, it can not possibly concur with the proposed change from the 1985 RsD of 0.006 pg/kg/day to 0.1 pg/kg/day.

The Panel's response to each of these points is described in more detail below:

### 3.1.1 The Adequacy of the Linearized Multistage model

The Panel agrees with the general thrust of the EPA Working Group's critique of the Linearized Multistage Model (see page 21), but would make the point more forcefully. In particular, the Committee believes that there are a number of models, in addition to the Linearized Multistage Model which incorporate the concept of low dose linearity. Some of these can also account for TCDD's promoting effects on the selective clonal expansion of preneoplastic foci. Further development and validation of these alternatives to the LMS model are needed and encouraged.

The Panel does agree that no validated model is available today to replace the LMS for calculation of an RsD for TCDD carcinogenesis.

### 3.1.2 The Availability of New Information For Use in the LMS Model

The Panel concurs that no new epidemiological or long term animal studies are available that would appropriately allow recalculation of the RsD using the linearized multistage model. However, the Panel wishes to emphasize the likelihood that epidemiological data may well become available in the near future, particularly if appropriate attention is paid to exposure and body burden.

### 3.1.3 Mechanistically Oriented Research

The Panel agrees that there is much exciting new information

concerning the mechanism of 2,3,7,8-TCDD carcinogenicity which is pertinent to regulatory approaches. It commends the Working Group for addressing this issue and for its careful and well-written review of the subject. In agreement with the EPA Working Group, the Panel believes that there is significant evidence supporting a receptor-mediated mechanism of TCDD toxicity. While a validated model of TCDD carcinogenesis based on a receptor-mediated mechanism is not now available, the Panel strongly recommends that such a model be developed as rapidly as feasible.

#### 3.1.4 Relaxation of the Risk Specific Dose for TCDD Carcinogenesis

A highly significant area of disagreement with the EPA Working Group is the Panel's failure to concur with the contention that a new model of TCDD carcinogenesis would necessarily lead to a relaxation of the existing RSD. Some members of the Committee were of the opinion that a receptor-based model could eventually support EPA's contention that the Linearized Multistage model overestimates the upper confidence limit for the carcinogenicity of TCDD (i.e. .006 is too stringent). Other committee members felt that it was not possible at present to predict whether the receptor-based model would lead to a less or more stringent RSD.

#### 3.1.5 Change of the Risk Specific Dose for TCDD Carcinogenesis

The Panel agrees with the EPA Working Group that there is currently no specific scientific pathway that would allow determination of the extent of change in the existing RSD for TCDD carcinogenesis. Accordingly, the Panel believes that at present there is no firm scientific basis for a change. In particular, as the Panel does not support the contention that a new model would necessarily result in a reduction in the stringency of the RSD, the Panel thus concludes that at the present time the important new scientific evidence about TCDD does not compel a change in the current assessment of the carcinogenic risk of dioxin to humans by the existing approach. EPA may for policy reasons set a different RSD for TCDD carcinogenesis, but the Panel finds no scientific basis for such a change at this time. The Panel does not exclude the possibility that the actual risks of dioxin-induced cancer for humans may be less than or greater than those currently estimated by the Agency using a linear extrapolation approach.

### 3.2. Comments on Specific Issues

#### 3.2.1 Mechanisms.

While there is still considerable uncertainty as to the

molecular events involved in TCDD induced cancer, and their relationship to current concepts of oncogenesis, the Panel concludes that it is likely that receptor-mediated mechanisms play a role in this process as in many of the biological effects of TCDD. Ligand recognition, receptor-ligand binding, stabilization of the receptor-ligand complex, translocation of the dioxin receptor (DxR) to the nucleus and binding DxR to specific DNA recognition sequences (suppressing or enhancing gene transcription) are steps which have been described in the receptor-mediated processes of cell response to TCDD. Although their relationship to TCDD carcinogenesis has not been clearly defined, these are likely to be early steps in the process. They may or may not be rate-limiting at low dose.

Consideration of this mechanism is useful for risk assessment for two reasons: (1) some data are available on the kinetics of these events, and (2) a fair amount of work has been done on modeling receptor-mediated events in biology (e.g. for instance, neurotransmitter receptors and steroid hormone receptors) -

The appropriateness of considering analogies to hormone receptors is supported by the following:

- a) the Ah receptor has a structural and functional resemblance homology to the glucocorticoid receptor
- b) the gene product of the Ah receptor is a regulatory protein as are the estrogen receptor and glucocorticoid receptor
- c) TCDD increases the effective concentration of Ah receptor
  - o Estradiol increases the concentration of estrogen receptor
  - o Glucocorticoids increase the concentration of glucocorticoid receptor
- d) The biological activity of hormone receptors is activated with only partial occupancy of the hormone responsive element on DNA (about 20%) and this is similar to the Ah receptor
- e) TCDD exposure may decrease the incidence of hormone-related tumors in rodents, which further supports a mediated role for carcinogenesis.
- f) TCDD modulates a variety of growth regulatory genes, including the estrogen and glucocorticoid receptors.

Modeling of receptor mediated event(s) follows the classic

linearized model of Lineweaver Burk kinetics. This requires the development (or refinement) of a biologically based model.

If this type of modeling is conducted it may lead to conclusion by some that a threshold exists. However, a receptor based model will be linear at low dose, when receptors are not saturated. As dose increases, receptor binding will be saturated, thus describing a curvilinear dose-response relationship.

It is also important to note that if TCDD is acting similarly (an agonist or antagonist) at the Ah receptor then there is likely to be partial occupancy by an "endogenous ligand" which means that receptor-mediated effects of TCDD may be additive to background.

### 3.2.2 Research Needs.

The Subpanel recommends the following research:

- a) more work understanding the biophysics of the interaction between dioxin and its receptor, and specific DNA recognition sequences - rate constants, equilibrium analyses, thermodynamics etc.
- b) role of receptor in carcinogenesis
- c) role of gene transcription in carcinogenesis
- d) relationship between receptor occupancy and gene products
- e) identification and function of the endogenous ligand
- f) role of steroid hormones in carcinogenesis
  - oncogenes and tumor suppressor genes (effects of glucocorticoids, estrogen and Ah receptor binding to DNA)
  - growth factors (oncogenes) and Ah receptor action
- g) A number of models, in addition to the LMS model incorporate the concept of low-dose linearity. Some of these can also account explicitly for TCDD's promoting effects on the selective clonal expansion of preneoplastic foci. Further development and validation of these alternatives to the LMS model are needed and encouraged.

### 3.2.3 Development and Selection of a Model.

Many of the toxic effects of TCDD, including tumor promotion, appear to be receptor-mediated. The dioxin receptor

which is closely related to many other proteins involved in growth control (e.g. glucocorticoid receptor, estrogen receptor, EGF receptor, nuclear thyroid hormone receptor, retinoic acid receptor, etc.) appears necessary, but not sufficient, for the responses. Tissue-specific factors, in addition to species-specific factors control the nature and the extent of these receptor-mediated responses. Thus, dose to the receptor only describes the first step in a complex process.

Nevertheless, it would be fruitful to develop a receptor-based model to describe the risk associated with dioxin exposure. Such a model would lead to testable hypotheses.

Mechanistically, all data to date are consistent with the concept that most, if not all, of the biological events, including tumor promotion, elicited by TCDD are mediated initially through the stereospecific binding of TCDD to a receptor protein and the subsequent modulation of gene expression. Evidence for this concept comes from a number of studies: genetic, structure-activity relations, and those examining the molecular interaction of the TCDD-receptor complex with specific responsive elements upstream from identified genes. This model is remarkably similar to that described for a number of hormonal systems, and in fact the Ah receptor has been suggested to be a member of a supergene family including the glucocorticoid, estrogen, and thyroid hormone receptors.

Based on the hypothesis that the binding of TCDD to the receptor may be the initial event in the biological responses to this compound, it may be possible to utilize receptor binding theory and/or actual binding kinetic data to derive a model that estimates a dose of TCDD necessary to produce a particular response. However, it should be recognized that there are likely to be a number of events subsequent to receptor binding which eventually lead to the final biological response, in this case tumor development or tumor suppression. Some of these events include binding of the ligand:receptor complex to specific DNA sequences as well as gene transcription and translation. Furthermore, there are likely to be a number of tissue- and developmentally specific regulatory factors, both positive and negative, that modulate these events. Some evidence for this has been presented, at least for the P450 gene. Receptor binding may or may not be the rate-limiting event in the processes leading to tumor development.

Classical receptor theory suggests that at low doses (concentrations) there will be a linear relationship between ligand concentration and binding. Thus receptor binding theory does not itself allow us to disassociate risk assessment from a low dose-linear model, nor does it allow us, at this time, to determine the slope of a dose-response curve for TCDD.

Although there are sufficient data indicating TCDD to have a potent tumor promoting ability, there are no conclusive data at this time to rule out the possibility of tumors being produced by other mechanisms. Furthermore, the definition of promotion, initiation, and progression are operational definitions not fully defining the actual mechanism by which these events occur. Thus, the present data do not imply the assumption that a threshold exists for TCDD.

#### 3.2.4 Toxicology of Related Compounds.

TCDD is only one member of a class of closely related molecules which appear to have similar effects and mechanisms of action. While the experimental animal data with the polychlorinated dibenzofurans, biphenyls, and other dibenzodioxins enhance the basic data base regarding TCDD toxicity, it is in the realm of human health effects following PCB and PCDF exposure that much can be learned. The Yusho and Yucheng cohorts have well characterized exposure to PCBs contaminated with PCDFs. Toxicity was correlated with the total furan exposure. The health effects-acute, long-term, reproductive - are well documented. For example, developmental toxicity clearly resulted from these exposures. This tells us that at equivalent TCDD exposure during development toxic effects will occur. Elevated incidences of tumors are being reported in Yusho (it is too soon for Yucheng). An epidemiological study of these cohorts might provide information on the risks of equivalent exposure.

#### 3.2.5 Epidemiology.

The Subpanel agreed with the conclusion expressed in the EPA document that the existing epidemiologic studies do not provide definitive data on health effects. The Subpanel views the human studies to date as inconclusive, due in most cases to design limitations such as inadequate power and inadequate exposure assessments. They are not suitable for inclusion in the 1988 Risk Assessment. Consequently, the Subpanel agreed that it is appropriate for EPA to continue to utilize animal toxicologic data.

The Subpanel noted that new human exposure data are available to the EPA for its consideration. Adipose and serum levels of 2,3,7,8-TCDD (lipid-adjusted) demonstrate that several levels of exposure are seen in human populations. In general, "unexposed" populations have been observed to have mean or median levels of 5 to 8 ppt, with most values under 20 ppt. The highest levels in humans have been seen in dioxin-exposed chemical production workers, who have current serum levels (lipid-adjusted) up to 1000 ppt, a mean of over 200 ppt, and who have had up to 14,000 ppt at last occupational exposure (under assumptions of a 78 year half-life and first order kinetics).

Current serum levels up to 300 ppt, with a mean of 49 ppt, have been observed in the U.S. Air force Ranch Hand pilots and mechanics. By contrast, in a recent CDC study the serum levels in 646 Vietnam ground troops were all below 20 ppt, with two exceptions of 20 and 45 ppt and a mean of 4.2 ppt.

Recognizing the importance of exposure measurements in human studies, the Subpanel suggested that some existing epidemiologic studies, such as the Air Force Ranch Hand study, might provide useful information on health outcomes if the existing data are reanalyzed according to new exposure information. The NIOSH mortality study of 7000 dioxin-exposed U.S. Chemical Workers and the medical study of a subset of these workers should provide useful information for the next EPA dioxin risk assessment. Because the evidence is that substantial exposure to Agent Orange did not occur on average for ground troops in Vietnam, studies of this group probably will not contribute useful information to dioxin risk assessments.

The Subpanel suggested that there may be value in considering whether existing studies might be analyzed together in a meta-analysis. The International Agency for Research on Cancer (IARC) has organized an International Dioxin Registry to compile data from studies of dioxin-exposed workers conducted in several countries in hopes of increasing statistical power for evaluation of rare outcomes in merged analyses. Data from this effort may contribute useful information in future risk analyses.

The Subpanel suggested that EPA consider whether the epidemiologic data from the Yusho and Yucheng populations might provide useful information for future risk assessments, since the effect of furans in animals are mechanistically like those of dioxins.

#### 3.2.6 Pharmacokinetics.

The Subpanel commended the EPA initial exploratory efforts in the area of pharmacokinetic modeling and encourages further work in this area.

#### 3.2.7 Reproduction and Immuno-Toxicity.

In the appendices to the document, EPA has provided short reviews of 2 other endpoints associated with TCDD, reproductive and immunotoxicity. By definition, however, these endpoints are excluded from the final discussion which is exclusively focused on cancer. The Subpanel has two comments on this general strategy: (1) the mechanisms of TCDD-induced reproductive and immunotoxicity may be relevant to understanding TCDD-induced carcinogenesis (for instance, oncogene activation, growth dysregulation, disrupted cell:cell communication, inhibition of immune surveillance), and (2) if the science eventually supports

a significant decrease in risk for cancer, it is critical that overemphasis on cancer (and risk management based on reducing cancer risk alone) does not result in a policy which might permit human exposures to TCDD in a range with potentially adverse effects on reproduction or possible immune function.

The Subpanel recommends that the appendices on reproductive and immunotoxicity be expanded to include relevant information on related compounds (dibenzofurans and PCBs) and that the mechanistic information be drawn out more specifically in the appendices and referred to in the main document.

#### 4.0 Comments on EPA's Draft Document. "Estimating Exposure to 2,3,7,8-TCDD"

Dr. Nancy Kim chaired the Dioxin Exposure Subpanel which also included: Dr. Edward Calabrese; Dr. Warren Crummet; Dr. Michael Gochfeld; Dr. Raymond Klicius; and Dr. Stephen Rappaport. Dr. Dennis Paustenbach, a member of the Subpanel who was unable to attend the meeting also contributed written comments on exposure as did Dr James Falco, a scientific advisor to the subpanel, and Dr Linda Birnbaum, a member of the cancer risk subpanel.

The Dioxin Exposure Subpanel's comments on EPA's draft "Estimating Exposure to 2,3,7,8-TCDD" appear below, where the document is referred to as the "exposure document." Page numbers and references are from the exposure document, except where otherwise noted.

##### 4.1 Overall Comments on EPA's Draft Exposure Document.

This update of 2,3,7,8-TCDD exposure document is an improvement over the earlier assessment because it includes new data, expands consideration of pathways, and addresses additional phenomena. It is a credible document and is one of the better exposure assessments. The important section on the uncertainty evaluation gives the reader an understanding about the magnitude of this factor.

The exposure document showed that indirect routes of exposure, that is dietary impacts, will usually predominate the level of risk for the general population. This hypothesis should be validated using environmental modeling and field measurements. EPA TCDD exposure assessments should focus on indirect sources of TCDD.

The exposure document's Executive Summary is excellent. Several points from that Executive Summary should be emphasized and reiterated throughout the report. For example, when assessing actual sites, whatever monitoring data are available should be used and are preferable to the estimation methods in

the document. The Subpanel emphatically agrees with this statement and recommends that this point be repeated throughout the document whenever appropriate. The Subpanel also recommends that the document point out that the best method of measuring human intake is to monitor people and that biological monitoring should be used when possible. These data will establish general exposure and identify subsets of the population (i.e., fish eaters, small children, people with pica) who may have elevated exposures above background.

#### 4.2 Comments on Specific Issues.

##### 4.2.1 Use the Best Data.

The Subpanel recommends that the document distinguish between excellent versus poor experimental work and thorough studies versus cursory examination. Not all data should be given the same weight. For example, the plant uptake data should be reviewed with this in mind. The conflict between data which are discussed may be because the radiolabelled TCDD used by Cicucci and Sacchi (pp. 44-45) may be only 60-80% pure as reported by Marple (p. 13). The Wipf data (p. 43) did not suffer from this shortcoming and the Subpanel recommends that these data be reviewed to consider weighing the Wipf data more heavily and revising the presentation of the Wipf data.

The data supporting appreciable uptake of TCDD by plants are weak. The soil-to-plant ratio data must be interpreted carefully, since this phenomenon is dependent on soil type and aging. Further, there may be a dramatic reduction in the relationship at very low levels such that as the concentration decreases, lesser amounts are available to be absorbed by the plant. The Subpanel recommends that the published work on the cyclodienes be reviewed to evaluate if plant uptake is likely to be less than estimated.

The uptake of TCDD by grazing animals (page 5) is perhaps the weakest discussion in the document. Dr. George Fries, USDA, has described an approach which may provide a good estimate of the magnitude of the exposure due to ingestion of food from grazing animals. The Subpanel recommends that this approach be included in the document.

##### 4.2.2 Pathways of Exposure.

The Subpanel recommends that a number of specific questions be addressed in the final report.

- a) Are TCDD concentrations higher on small particulates which may be poorly captured by air pollution control devices?
- b) What is the impact of declining performance or

efficiency of pollution control devices on removal of TCDD and related compounds?

- c) Is it generally accepted that dynamics of TCDD in wet soil are described by Henry's Law?
- d) What is the significance of identifying a small proportion of the population with high exposure (i.e., the limited number of children with pica eating 7g of soil per day)?
- e) Are photolysis and vapor phase diffusion, rather than runoff, the major processes for mobilization from soil?
- f) What is the impact of the environmental fate of TCDD in soil and fly ash?

#### 4.2.3 Indirect Exposure.

The modeling activities in the exposure document clearly imply that indirect routes of exposure (dietary impacts) appear to predominate. This can be seen in Tables 6-6 and 6-16 which show that, in all scenarios which consider dietary sources, the ingestion of beef, fish, and dairy products contributed more than 82% of the total exposure.

The Subpanel makes two recommendations regarding this important implication. First, the Agency should validate the modeling outcomes with environmental monitoring. Sensitivity analyses should be conducted to prioritize the various data gaps prior to undertaking such monitoring studies. To improve understanding of indirect exposure to 2,3,7,8-TCDD, it (and perhaps its congeners) should be added to the market-basket survey. Second, the revised document should conclude that exposure assessments should particularly focus upon indirect sources of TCDD.

The exposure scenarios generally concentrated on average estimates. The Subpanel recommends that the revised document discuss the potential for two different types of situations which could lead to much higher exposures than the average. One situation is illustrated by the pica child or adult. Average soil ingestion levels were used in estimating soil exposures, but this subpopulation may have exposures which are more than one-hundred times greater than the average. The second situation would involve a dramatic increase in exposure. For example, an individual who ingests a highly contaminated fish may have a pulse exposure which would be orders of magnitude higher than the average daily exposure. The size of each population should be estimated.

#### 4.2.4 Scenarios.

The two incinerator cases in scenarios 16 to 19 should be reevaluated using other data because neither case represents an average existing plant nor a new modern state-of-the-art facility. The case of 120 tons per day (TPD) uses the worst data ever measured (pp. 214-215) and the 3,000 TPD case represents a plant with either poor operation practices or ineffective air pollution control devices.

The 120 TPD plant, the Hampton data of 0.289 ug/kg, represents the very worst data ever measured and this point should be stated up front on page 208 and page 219. The justification on page 299 for its use is no longer valid because the data by Hay, et al, on page 214, were in error by a factor of 1,000, due to a typographical error in the Chemosphere paper (see original EPS 3/UP/1 report). The emission factor should be reconsidered and lowered for the 120 TPD plant.

Furthermore, the emission factor of 0.001 milligrams per kilogram (ug/kg) for the 3,000 TPD plant should be lowered. On page 215, several plants show lower values; namely 0.000371 ug/kg for Marion County and 0.000056 ug/kg for Wurzburg. These are state-of-the-art facilities with scrubber/fabric filter air pollution control systems. EPA has data from other plants to substantiate that a lower level of emissions is appropriate for a new modern incinerator.

The dispersion modeling for the incinerator emissions assumed a stack height equivalent to adjacent building height (p. 223). This is not representative of typical construction, certainly not for a new modern facility. As an absolute worst case, one can justify using this assumption for the 120 TPD case. However, this assumption is not appropriate for a modern plant, where stack height is normally selected to significantly exceed adjacent building heights to avoid plume downwash effect. A factor should be provided (p. 301) in the discussion of uncertainty to provide the reader with an appreciation of the beneficial effect of a proper stack height.

In addition, the pictorial representation of an incinerator with tall stack on p. 211 misrepresents the actual assumption used. A stub stack equal to building height should be shown unless the assumption is altered to provide a tall stack that is well above adjacent building height.

In terms of modeled phenomena, off-site volatilization of TCDD from surface particulates transported to fields through surface erosion or deposition of airborne TCDD vapor and TCDD-contaminated particles are not explicitly considered. Although in the case of the incinerator assessment, an empirical deposition rate is estimated.

The Subpanel recommends that volatilization be explicitly accounted for in off-site as well as on-site analysis. This will avoid bias which could inflate dairy and beef ingestion related exposures. It would also insure consistency of analysis across exposure estimates.

Partitioning phenomena between vapor phase and particulate-bound TCDD in air and dissolved and particulate-bound TCDD are not defined. Since the environmental behavior is dependent on the extent of partitioning, it is recommended that development of descriptions of these phenomena be undertaken.

The dilution of deposited TCDD-contaminated particulate with uncontaminated soil is not calculated. A mixing depth for particulates of 1 cm top soil (stated on p. 239) is presented without justification. The revised exposure document should include basis for the selection of this specific depth. Research to develop a dilution model analogous to the mixing model developed for dilution of land-eroded particulates should be carried out so that parallel phenomena are treated in like manner.

#### 4.2.5 Exposure and Epidemiology.

Epidemiology studies of human populations have yielded little information on health effects, but are a fruitful source of information on human exposure. Improved understanding of exposure is essential for designing studies of human health affects. This is very clear in the targeting of herbicide manufacturing workers. It is also clear that studies of Vietnam veterans as a group have failed because of lack of good exposure data. Epidemiological studies of veterans or other occupational groups with known and adequate exposure data should be pursued. However, the Subpanel recommends that the exposure document emphasize that without good exposure data, the epidemiologic studies are meaningless.

#### 4.2.6 Estimating Exposures in the Absence of Empirical Data

The document provided exposure estimates in the absence of reliable empirical data. In the absence of data, any approach that is proposed cannot be refuted or validated. The Subpanel recommends that the reader be alerted when an estimate from a given pathway has a particularly large uncertainty associated with it and that the document note that an exposure estimate may be too uncertain to be reliable. The exposure document only reaches this latter conclusion for plant uptake of 2,3,7,8-TCDD (pp. 45, 205) after opining that the plant uptake data were conflicting. (The problems with the plant uptake data are discussed in detail under section 2.2.2.)

The data on the division of 2,3,7,8-TCDD emissions between the vapor and particulate phase is also weak. The Subpanel recommends that the reader be specifically alerted to the particular weakness in scenarios using these data.

On page 220 the exposure document states, "There are virtually no data concerning the division of 2,3,7,8-TCDD emissions between the vapor and particulate phase for stack emissions in the U.S.A." From the foregoing quotes, it is apparent that the authors of this exposure document are not sure what percentage of 2,3,7,8-TCDD from incinerator stack emissions is in the vapor or particulate phase. Nevertheless, the exposure document states on page 220: "For our scenarios we assumed 63% to be in the vapor phase and 37% particulate, since these values are reported in two studies (Hagenmeier et al., 1985; Scheidl et al., 1985)." In Hagenmeier, et al, various sampling methods for PCDD and PCDFs in stack gases were compared. It specifically stated that "the distribution of PCDD/PCDF between filter dust, condensate and impinger does not allow to distinguish between particle bound and gaseous PCDD and PCDF in the stack gas."

It is also impossible to determine the distribution of 2,3,7,8-TCDD released from incinerators in the vapor and particulate phases based on information on the release of total CDDs in the vapor and particulate phases since 2,3,7,8-TCDD makes up such a small fraction of all CDDs released (cf. Table 6-27).

Other exposure estimates which are based on little or no data include: (1) vapor inhalation from landfill or contaminated soil scenarios, and (2) all pathways from incinerator fly ash stack emissions.

#### 4.2.7 Rely More on Field Sampling Data and Less on Dispersion Modeling Results

The Executive Summary of the exposure document (p. 1) states: "It should be emphasized that when assessing particular sites, monitoring data may be available, or measurements may be made, that would preclude the necessity of part or all of the estimation methods described here." This essential principle receives very little attention throughout the development of this exposure document. While it is mentioned several times in the exposure document, the emphasis is clearly on developing an approach to estimating exposures regardless of how much data are available.

An example of a particular problem is the exposure estimate to 2,3,7,8-TCDD from incinerator fly ash, which was deposited on cattle fodder, which was consumed by beef cattle which were subsequently ingested. If EPA were presented with such an estimate, it would probably instruct the submitter to "measure"

the level that is present in the beef. In short, so many assumptions must be made to estimate human exposure 2,3,7,8-TCDD from beef derived from cattle ingesting fodder contaminated with 2,3,7,8-TCDD on fly ash that the reliability of such an exercise is seriously questioned and the Subpanel recommends that this be highlighted in the document. A preferable alternative approach to exposure estimation would be to measure the level of 2,3,7,8-TCDD in the matrix of concern (in the above example, in beef) and then to proceed with the exposure assessment.

#### 4.2.8 Verifiable Exposure Estimates.

The exposure estimates rely heavily on dispersion models and exposure parameter values that are highly dependent on site-specific characteristics. Further, a critical factor like deposition velocity of particles receives little attention as does estimating the concentration of 2,3,7,8-TCDD in a particular matrix. If field sampling data are available and if they correspond to the modeled values, one does not know whether this is because all the attendant uncertainties canceled each other out or whether the modeled values were indeed "accurate." The Subpanel recommends that research be undertaken to verify and improve the modelling estimates.

#### 4.2.9 Incorporation of the Most Reliable Exposure Assessment Information

The exposure document should include information on the low bioavailability of 2,3,7,8-TCDD on fly ash as compared to soil in those scenarios which assess exposure to fly ash. The work of van de Berg, et al (1983, 1985), is cited which suggests a lower bioavailability of 2,3,7,8-TCDD from fly ash than from soil.

#### 4.1.10 Rigorous Characterization of Uncertainty.

The exposure document presents its uncertainty analysis in Chapter 7. The Subpanel commends the Agency for the detailed presentation on uncertainty. This characterization is an important element in the risk assessment process and the Agency has done a commendable job in this particular document.

In Tables 7-1 to 7-17, the uncertainty analysis of some parameter variables for various exposure pathways is given. For example, Table 7-1 on soil dilution factor presents uncertainties for three parameters: "quantity of erosion from contaminated area", "quantity of eroded soil deposited on adjacent field", and "mathematical model to assess the rate of 2,3,7,8-TCDD in soil placed on adjacent field". The Subpanel recommends that uncertainties surrounding other variables, such as soil characteristics, land use, climatological conditions, and how the landfill is contaminated with 2,3,7,8-TCDD, be addressed.

The exposure document's uncertainty analysis should also be made more quantitative. Instead of indicating that the quantity of erosion from the contaminated area ranges between 0.6 and 306 tons per acre-year and that the value used was 65 tons per acre-year, the Subpanel recommends that the exposure document state the uncertainty in terms of a deviation. By stating the uncertainty of each parameter value in this manner, the magnitude of the uncertainty for the entire exposure assessment can be determined by multiplying the uncertainty factor of each parameter. In addition, the parameters that "drive" the exposure assessment could be identified and prioritized for verification with field sampling results.

#### 4.2.11 Pharmacokinetics.

The exposure document outlines two pharmacokinetic approaches for relating exposure with tissue levels of TCDD. The first, referred to as the "Commoner Approach," is described on pp. 128-130. It refers to the use of a single-compartment open model with first-order elimination to describe TCDD disposition in the body; this model was presented by Commoner, et al, at two symposia in 1985-86. Although the model itself is straightforward, several errors in developing equations (5-1) to (5-4) detract from the description.

The Subpanel recommends that the document be corrected either to be consistent with the treatment of Commoner, et al, or to follow a similar approach which employs other constants which may be desired. For example, the agency may wish to include an absorption factor to account for fractional bioavailability.

The second pharmacokinetic approach outlined in pp. 130-137 describes development of a physiologically based pharmacokinetic model (PBPK) where none currently exists. The document suggests that one such model developed for 2,3,7,8-TCDF by King, et al (1983), may be adapted to TCDD. While the tissue compartments, volumes, and perfusion rates of the King's model may be appropriate for TCDD, the binding and metabolism of TCDD may be sufficiently different from that of TCDF to require a somewhat different structure. Furthermore, because the half life of TCDD in humans is greater than that predicted from observations in the rat, it may not be possible to rely entirely upon rodent species in developing such a PBPK model. The Subpanel agrees with the Agency that development of a PBPK model for TCDD is an important task which should be pursued with high priority. However, the Subpanel recommends that these potential limitations be included in the document.

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